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CASE REPORT

Extracutaneous involvement of subcutaneous panniculitis-like T-cell lymphoma associated with hemophagocytic lymphohistiocytosis and refractory to intensive chemotherapy

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Abstract

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is an uncommon primary cutaneous lymphoma characterized by subcutaneous infiltration of mature cytotoxic T-cells with rearranged alpha/beta T-cell receptor phenotype. SPTCL is typically a disease of young adults with 36 years old being the median age. Patients commonly present with B-symptoms and multiple painless skin nodules in the extremities and trunk. Extracutaneous involvement is rare. Here, we present a case of SPTCL in a 32-year-old woman with diffuse but clinically occult skin lesions detected on imaging through multiple modalities and pathology-proven extracutaneous involvement in the mesentery. Retrospective chart review, review of patient specimens, and literature review for similar cases were performed. Histologic examination revealed SPTCL in the skin and omentum. Our patient's clinical course was associated with hemophagocytic lymphohistiocytosis (HLH), a known poor prognostic indicator, and refractoriness to intensive chemotherapy. Due to the rarity of this disease, treatment is not yet standardized. However, for our patient, an allogeneic stem-cell transplant resulted in positron emission tomography/computed tomography-negative remission 11 months post-transplant or 20 months post-initial presentation. We report an unusual case of subcutaneous panniculitis-like T-cell lymphoma (SPTCL) with clinically occult subcutaneous lesions and prominent biopsy-proven extracutaneous mesenteric involvement. Further investigation is required to better understand the mechanism of disease, prognosis, and optimal treatment approach for SPTCL patients presenting with extracutaneous involvement and HLH.

Keywords Subcutaneous panniculitis-like T-cell lymphoma · Hemophagocytic lymphohistiocytosis · Extracutaneous involvement · Refractory to chemotherapy · Stem-cell transplant

Introduction

Subcutaneous panniculitis-like T cell lymphoma (SPTCL) is a rare non-Hodgkin lymphoma initially described by Gonzales et al. in 1991 [1], characterized by preferential infiltration of neoplastic, CD8 + cytotoxic T-cells in the subcutaneous adipose tissues [2]. Typically, the lesions are identified as cutaneous nodular lesions in the extremities and trunk, with extracutaneous findings rarely described [2, 3]. Histologically, a lymphohistiocytic infiltration in lobular pattern and characteristic rimming of adipocytes is seen, mimicking panniculitis [4]. Clinical course is typically indolent, though a significant subset develops hemophagocytic lymphohistiocytosis (HLH) which has been associated with poorer prognosis [1].

Clinical history

A 32-year-old woman with a medical history significant for unilateral ovarian cystectomy presented to internal medicine for a 2-month history of fever, night sweats, weight loss, and nonspecific abdominal discomfort. Initial laboratory findings showed increased CRP (72.1 mg/L), isolated lymphopenia (0.7×10^9/L), and elevated aspartate transaminase (80 U/L, upper limit 40 U/L). There was no clinical or laboratory evidence of systemic lupus erythematosus or other rheumatologic conditions. CT and MR imaging revealed punctate liver lesions, nodular omental

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thickening, and multiple subcutaneous flank lesions, concerning for possible disseminated miliary tuberculosis; however, infectious work-up was negative. Subcutaneous lesions were not apparent on initial clinical exam. PET/CT confirmed the previous imaging findings, but also revealed additional innumerable subcutaneous foci of hypermetabolic nodularity with ground-glass appearance throughout the gluteal region, upper extremities, back, abdomen, and thighs bilaterally; multiple foci in intraabdominal and retroperitoneal fat; and hypermetabolism within the ascending colon. Nodal involvement was not evident. Colonoscopy and colonic biopsies were negative for malignancy. Core biopsies targeting the lower flank subcutaneous area showed an atypical lymphoid infiltrate, insufficient for definitive diagnosis.

After a brief discharge from hospital, the patient was re-admitted with high fever (41 °C) and clinical deterioration. Her clinical and laboratory findings met the criteria for hemophagocytic lymphohistiocytosis (HLH): hyperferritinemia (18,538 µg/L), marked anemia (65 g/L), neutropenia (0.7×10^9/L), hypertriglyceridemia (2.53 mmol/L), hypofibrinogenemia (0.7 g/L), elevated sIL-2 receptor (sCD25) levels (3980 U/mL, reference range 278–1580 U/mL), increasing hepatomegaly, and bone marrow findings of hemophagocytosis. Omental and repeat skin biopsies were performed to identify the underlying etiology, and revealed the pathological diagnosis of subcutaneous panniculitis-like T-cell lymphoma (SPTCL). Bone marrow aspirate and biopsy were not involved.

Methods

Retrospective chart review and review of patient specimens were performed for this case report.

Pertinent human medical literature in the English language up to January 2021 was identified through a Medline (PubMed) computerized literature search using the following keyword: subcutaneous panniculitis-like T-cell lymphoma. The primary search yielded 287 articles, all were manually reviewed. Studies with a histologic diagnosis of SPTCL with biopsy-proven or suspected extracutaneous non-marrow fat involvement were included. Two cases with non-diagnostic biopsies, four cases with extracutaneous involvement on relapse post-chemotherapy, two articles where full text was not readily available, and cases with TCRγδ rearrangement were excluded. The reference lists of articles found through the search were also reviewed for relevant articles.

Results

The following specimens were examined. Immunohistochemistry findings are as listed in Table 1.

Specimen A Left lower flank core biopsies were obtained, measuring between 0.1 and 1.1 cm. These biopsies contained scant fibrofatty subcutaneous tissue with pannicular lymphohistiocytic infiltrate. The infiltrate featured small to intermediate-sized T-lymphocytes with hyperchromasia and some apoptosis. No mitotic figures were seen. The case was reviewed by dermatopathology and hematopathology consultants because of the atypical T-cell infiltrate, but there was insufficient tissue for definitive diagnosis of a T-cell lymphoproliferative disorder; additional tissue was requested.

Specimen B Excisional biopsies of omentum were performed. The larger biopsy specimen measured $4.7 \times 3.5 \times 0.5$ cm and was initially interpreted as focal panniculitis. However, the case was later re-examined following the repeat skin biopsy (findings described below) and found to have abnormal patchy lymphocytic infiltrates (see Fig. 1). The smaller omental specimen measured $2.2 \times 0.9 \times 0.3$ cm consisted of non-necrotizing granulomas with multinucleated giant cells, focal hemosiderin deposition, and patchy fibrosis. Auramine/rhodamine stain was negative for acid-fast bacilli. T-cell receptor (TCR) gene rearrangement molecular assays were performed which showed polyclonal TCRγ and TCRβ. Flow cytometry specimen was paucicellular and insufficient for phenotypic assessment.

Specimen C Left lower back skin punch biopsy measuring 0.5×0.9 cm showed prominent lymphohistiocytic infiltrates consisting of small to intermediate-sized T-lymphocytes with hyperchromasia and nuclear irregularity in the subcutaneous adipose tissue only, sparing the epidermis and dermis. Karyorrhexis, abnormal mitotic figures, and enlarged histiocytes with hemophagocytosis (see Figs. 1 and 2) were noted.

Table 1 Summary of immunohistochemistry studies showing immunophenotype of the lymphoma cells

Specimen	Immunohistochemistry findings										
	CD3	CD4	CD8	CD2	CD5	CD7	CD56	TIA-1	Granzyme B	Ki67	CD20
A. Left lower flank	+	−	+	NC	+/−	NC	−	+	+	30–40%	−
B. Omentum	+	−	+	+	+	+	−	+	+	20–30%	−
C. Left lower back	+	−	+	+	+/−	+/−	−	+	+	20–30%	−

Stains performed but not assessable due to tissue exhaust are listed as non-contributory (NC); positive (+), negative (−), subset loss (+/−)

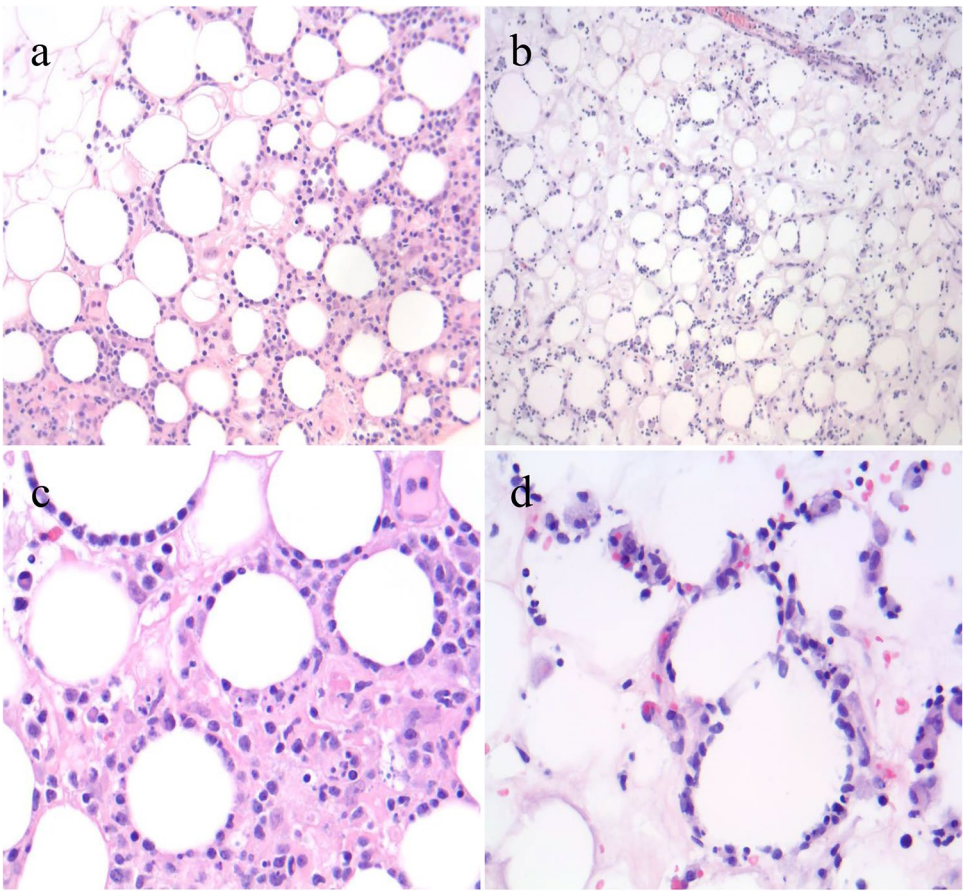

Fig. 1 **a** Omentum biopsy (specimen B) hematoxylin and eosin (H&E), × 100, showing patchy pannicular involvement. **b** Left lower back biopsy (specimen C) H&E, × 100. **c** Omentum biopsy H&E, × 500, showing lymphocytic rimming of adipocytes. **d** Left lower back H&E, × 500, showing rimming and hemophagocytosis

Flow cytometry was paucicellular, and showed poor viability and non-contributory. TCRγ showed prominent peaks, but TCRβ evaluation was limited by poor amplification. TCRβF1 staining by immunohistochemistry was positive.

Based on the morphological, immunohistochemical, and molecular findings of the omental and skin biopsies, a diagnosis of SPTCL with subcutaneous involvement was made.

The patient underwent six cycles of intensive CHOEP (cyclophosphamide, doxorubicin, etoposide, vincristine, and prednisone) chemotherapy with partial response initially. However, her hypermetabolic subcutaneous nodularity was found to have increased on PET/CT 6 months following initial diagnosis (Fig. 3), indicating refractoriness to multi-agent chemotherapy. Due to disease progression and ongoing clinical signs and symptoms of HLH, six cycles of salvage chemotherapy GDP (gemcitabine, dexamethasone, cisplatin) were given which achieved PET-negative remission. Treatment was complicated by severe cytomegalovirus (CMV) retinitis. Subsequently, a matched sibling allogeneic stem cell transplant was performed. Patient remains in PET and clinical remission at last follow-up, 11 months post-transplant or 20 months post-initial presentation.

Discussion

After the initial report by Gonzales et al. in 1991, SPTCL was defined by the European Organization for Research and Treatment of Cancer (EORTC) in 1997 [3], recognized by the World Health organization (WHO) in 2001, and subsequently, the entity of TCRαβ SPTCL was differentiated from the more aggressive and provisional category of primary cutaneous γδ T-cell lymphoma (PCGD-TCL, previously TCRγδ SPTCL) in the WHO 2008 revision [2, 4]. Prior to the 2008 classification, SPTCL was estimated to comprise less than 1% of all non-Hodgkin lymphomas and 5% of all primary cutaneous lymphomas [3]; hence, the true incidence is likely lower. The median age of presentation is 36 years of age, with a female predominance (male-to-female ratio of 0.5) [3]. Patients commonly present with multiple painless subcutaneous nodules or deep-seated plaques primarily in the extremities and trunk [3]. Ulceration is rare, in contrast to PCGD-TCL [3]. In addition, symptoms of fever, chills, night sweats, weight loss, and myalgias are common [3, 4].

Morphologically, SPTCL presents as lymphoid infiltrates in a predominantly lobular pattern with admixed histiocytes, primarily restricted to the subcutis. Lymphocytes show

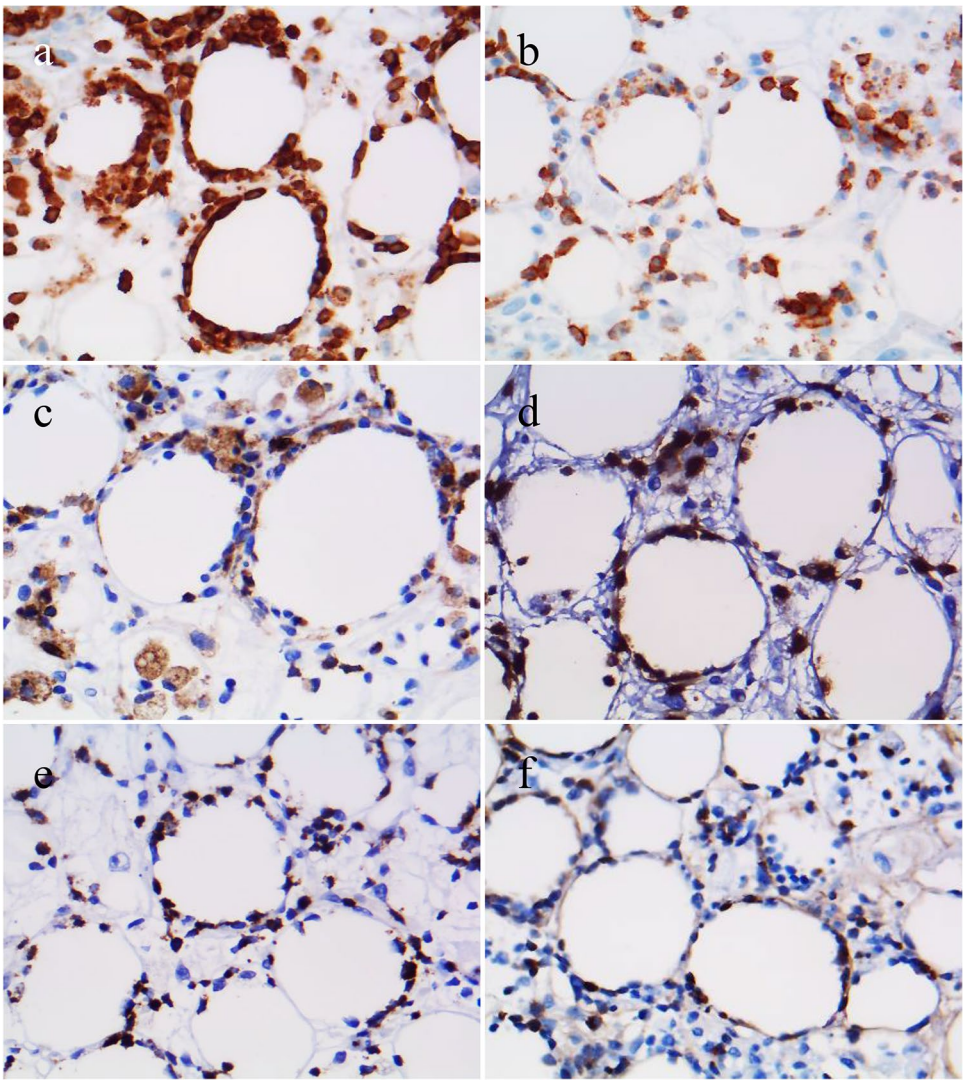

Fig. 2 Left lower back biopsy (specimen C), ×400. **a** CD3. **b** CD5 showing subset loss. **c** CD4 staining predominantly histiocytes. **d** CD8. **e** TIA-1. **f** granzyme B

slight atypia, such as hyperchromatic nuclei, mild pleomorphism, and increased proliferation rate; Ki67 is generally greater than 25%. Adipocyte rimming by the neoplastic cells is a characteristic finding of SPTCL, but not pathognomonic as it can be seen in other cutaneous lymphomas and lobular panniculitis [3]. The difficulty of diagnosing SPTCL in small samples or samples that may not contain much subcutaneous tissue is known and scant sampling of lymphocytic lobular panniculitis may present significant challenges in differentiating a benign chronic inflammatory reaction from a lymphoproliferative process [5], as seen in the initial biopsy in this case. Typically, immunohistochemistry in SPTCL shows cytotoxic T-cells staining pattern with CD3+, CD4-, CD8+, CD56-, and TIA-1/perforin/granzyme B positivity [6]. T-cell antigens of CD2, CD5, and CD7 are variably lost, at 10%, 50%, and 44%, respectively [6]. EBV, whether by viral detection or in situ hybridization, is typically negative and does not appear to play a role in pathogenesis [1, 4]. Histologic correlation with the patient age, clinical symptoms, imaging findings, and with ancillary testing is often needed for accurate diagnosis of SPTCL.

There are a number of differential diagnostic considerations. In about 20% of cases, SPTCL is associated with autoimmune diseases, such as systemic lupus erythematosus (SLE); hence, lupus erythematosus panniculitis (LEP) is important to exclude [4]. LEP generally presents with clinical symptoms fulfilling rheumatological criteria of SLE, and shows morphological features such as vacuolar interphase change, abundant interstitial mucin deposition, and other features similar to a reactive benign panniculitis such as predominance of CD4+cells and admixed B-cells and B-cell aggregates, without T-cell rimming of adipocytes. Nevertheless, some have suggested at least some degree of overlap between LEP and SPTCL, and propose a potential descriptive diagnosis of atypical lymphocytic lobular panniculitis in equivocal cases [7]. Other differential diagnoses

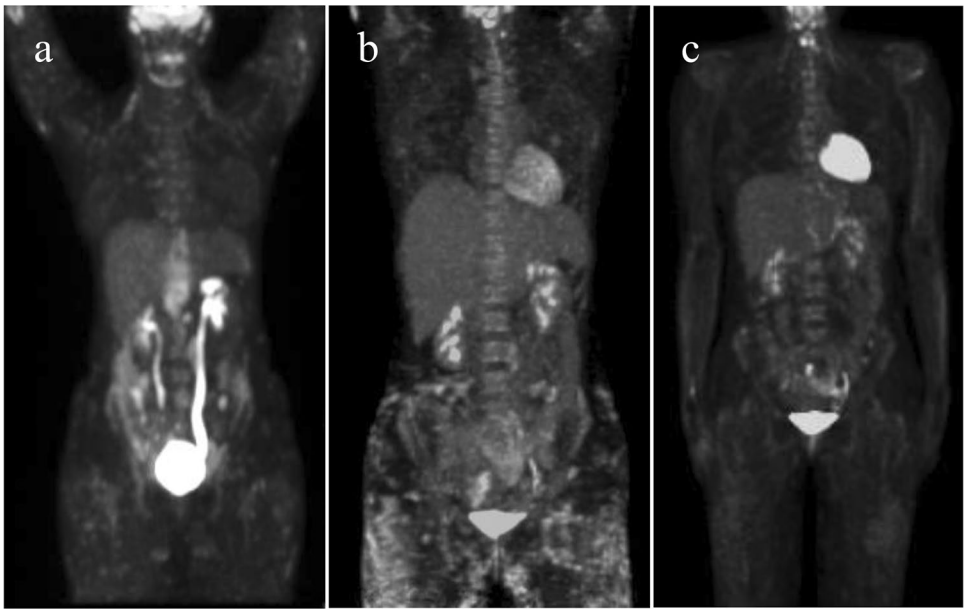

Fig. 3 **a** PET/CT at diagnosis showing innumerable foci of fat stranding with low metabolic activity within subcutaneous fat, intra-abdominal fat, and retroperitoneal fat. **b** PET/CT post-CHOEP chemotherapy showing interval progression of hypermetabolic subcutaneous nodularity, most pronounced in bilateral gluteal regions, thighs, and partially imaged arms. **c** PET/CT post-allogeneic stem cell transplant showing less prominent low-level uptake within subcutaneous fat stranding in proximal upper and lower extremities, Deuville 2

include primary cutaneous natural killer-like T-cell lymphoma which is CD56+, predominantly dermal, and with EBV positivity; or other cutaneous lymphomas which generally present in dense sheets of lymphoid infiltrates without rimming of fat spaces [3].

We found a CD8+ predominance in our malignant T-cell population, which is the typical finding in SPTCL. Initially other CD4/CD8 expression patterns were described to occur in TCRγδ SPTCL/PCGD-TCL, particularly of the CD4-/CD8- double negative phenotype [1]. At times, CD4/CD8 were indeterminate in TCRαβ SPTCL [6]. Rare cases of peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS) with SPTCL features [8] and SPTCL with CD4+/CD8- phenotypes, are described [9–11]; in the latter case series, the inclusion of cases with TCRγδ gene rearrangement raises the question whether those cases truly demonstrate a rare CD4+ variant of TCRαβ SPTCL or would now be more correctly categorized in the provisional PCGD-TCL by strict WHO (2008)-EORTC criteria. In our case, the TCRβ assay did not demonstrate a clonal TCRβ population but TCRβF1 staining was positive, ruling out PCGD-TCL. Furthermore, the more prominent subcutaneous involvement (in comparison to the extracutaneous tissue), absence of dermal/epidermal involvement, and lack of ulceration (more commonly seen in PCGD-TCL [2, 4]) supported this distinction.

Although generally considered indolent, SPTCL has been associated with hemophagocytic lymphohistiocytosis (HLH) in 15–20% of patients, which is associated with poorer prognosis [1]. However, this association may be overestimated as initial studies included PCGD-TCL. The diagnosis of non-hereditary HLH is based on presence of at least five of eight signs: fever, splenomegaly, cytopenias (two or more lineages), hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis, low/absent natural-killer-cell-activity, hyperferritinemia, and increased soluble interleukin-2-receptor levels [12]. Aside from rare lymphadenopathy, bone marrow involvement, and/or hepatosplenomegaly (the latter may be attributed to HLH itself), overt extracutaneous adipocyte involvement is considered unusual, with none reported in the initial large cohort of 83 described by EORTC [3]. Four cases in the literature describe initial presentations of biopsy-proven intra-abdominal involvement and all of these were associated with HLH or poorer response to multi-agent chemotherapy [13–16]. One case with probable mesenteric involvement identified with MRI developed HLH requiring autologous stem cell transplant [17]. Given the universally poorer response of the histology-proven cases in literature (see Table 2), biopsy of suspected extracutaenous involvement may be helpful in prognostication. Positron emission tomography (PET) has been utilized to identify occult extracutaneous involvement/dissemination [18–20], some associated with aggressive clinical course [19, 20]. Imaging was instrumental in our case as the skin lesions were clinically occult. In our patient, the clonal relationship between the subcutis and omental lymphoma involvement was not definitively established, as the omental polyclonal TCR assay may be a false negative due to the scant infiltrate and the repeat skin biopsy TCR assay was indeterminate. However, the findings were diagnostically consistent with the same disease due to the similarities in morphology, immunohistochemistry, and imaging findings.

Table 2 Summary of biopsy-proven or suspected intra-abdominal SPTCL involvement

#	Citation	Demo	Initial distribution (denotes suspected involvement, not biopsied)	HLH	Treatment	Outcome
1	Wang et al., [13]	**38 M**	**Subcutaneous abdominal wall, inguinal peri-nodal adipose tissue, mesentery (hepatosplenomegaly)**	**No**	**EPOCH × 2 cycles, ICE × 2, hyper-CVAD**	**Pending autologous stem cell transplant**
2	**Lester et al.,** [14]	**33 M**	**Subcutaneous lower back, mesentery/omentum**	**Yes**	**CHOEP × 1, further multi-agent chemotherapy unspecified, allogeneic stem cell transplant**	**Status post-allogeneic stem cell transplant**
3	**Hrudla et al.,** [15]	**65 M**	**Mesocolon adipose mass**	**Yes**	**NA**	**Diagnosed on autopsy**
4	**Wegehaupt et al.,** [16]	**17 M**	**Mesentery (subcutaneous right thigh/hip, splenomegaly)**	**Yes**	**Etoposide-based HLH-2004 protocol, CHOP × 1, DHAP × 2, VIP-E × 1, FBT followed by allogeneic stem cell transplant**	**Relapse 8 years after initial treatment**
5	Giza et al., [17]	35 M	Supraclavicular peri-nodal adipose tissue (hepatosplenomegaly, mesentery)	Yes	CHOEP × 6, BEAM followed by autologous stem cell transplant	PET-negative 3 months post-transplant
6	Mitsuhashi et al., [18]	43F	Subcutaneous lower extremity (inguinal lymph nodes, intra-abdominal fat)	No	CHOP × 6	PET-negative post-chemotherapy
7	Gorodetskiy et al., [19]	27F	Unspecified skin (head, neck, upper extremities, chest, breasts, mesocolon)	No	CHOP × 6, GEMP × 6	Complete remission, 29 months follow-up
8	Gorodetskiy et al., [19]	53F	Unspecified skin (head, trunk, upper and lower extremities, epiploon in the left mesogastric area)	No	FCM × 3, GEMP × 6	Complete remission, 8 months follow-up
9	Shen et al., [20]	32 M	Subcutaneous abdominal (subcutaneous, intermuscular fat of the left superior chest wall, extra-pleural and extra-peritoneal fat, right intra-renal dispose capsule, mesentery of the colorectum)	No	Pegaspargase with CDOP × 2, CHOPE × 2, GDP × 2, CMD × 3, oral chidamide × 6 months	No treatment 18 months follow-up

Cases 1–4, bolded, are biopsy-proven extracutaneous involvement

F, female; *M*, male; *NA*, not available; *EPOCH*, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; *ICE*, ifosfamide, carboplatin, and etoposide; *hyperCVAD*, cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and cytarabine; *CHOEP*, cyclophosphamide, doxorubicine, vincristine, etoposide, and prednisolone; *DHAP*, dexamethasone, cytarabine, cisplatin; *VIP-E*, etoposide, ifosfamide, cisplatin, epirubicin; *FBT*, fludarabine, BCNU, thiotepa; *BEAM*, carmustine, etoposide, cytarabine, and melphalan; *CHOP*, cyclophosphamide, doxorubicine, vincristine, and prednisolone; *FCM*, fludarabine, mitoxantrone, and cyclophosphamide; *GEMP*, gemcitabine, cisplatin, and methylprednisolone; *CDOP*, vindesine, cyclophosphamide, doxorubicin, prednisone; *CHOPE*, etoposide, vindesine, cyclophosphamide, doxorubicin, dexamethasone; *GDP*, cisplatin, dexamethasone, gemcitabine; *CMD*, cladribine, mitoxantrone, dexamethasone

There is no standardized therapeutic approach for treatment of SPTCL, which may include radiation therapy for localized disease, immunosuppression, and multi-agent chemotherapy. Treatment of SPTCL without associated HLH may be successful with prednisone or other immunosuppressive agents. For SPTCL with HLH, intensive multi-agent CHOP or CHOP-like chemotherapy with auto or allogeneic stem cell transplant are often attempted for curative intent [3, 4]. Because so many SPTCL patients are young, another important consideration prior to treatment requiring chemotherapy or pelvic radiation is fertility conservation; fertility may or may not return after intensive therapy. Our patient developed rapid clinical deterioration with 5/8 of the HLH criteria, further confirming associated HLH. Subsequently, chemotherapy refractoriness was observed, requiring additional salvage chemotherapy and stem-cell transplant.

T-cell lymphoma comprises approximately 35% of the etiology of acquired HLH, with postulated mechanism being a defect in granule mediated-cytotoxicity, uncontrolled T-cell activation, and cytokine storm [21]. Although panniculitis-like T-cell lymphoma (including PCGD-TCL) is known to be associated with a higher risk of HLH [21], it is unclear what specific mechanism drives the development of extracutaneous dissemination, HLH, and poorer prognosis in this subset of SPTCL. Due to the rarity of this entity, molecular analysis beyond TCR rearrangements is scarce. In a case series assessing genetic variants of 27 patients with SPTCL limited to the subcutis, 16 harbored alteration in *HAVCR2*, a gene that encodes for T cell immunoglobulin mucin 3 (TIM-3), which appeared to be found in SPTCL associated with HLH. This supported an immune dysregulation etiology and providing evidence, even in HLH-associated cases, for potential immunosuppressive or immunoregulatory therapeutic targeting in the future [22]. Mutation in TIM-3 has been reported in a case of primary mesenteric presentation with HLH and recurrence [16], suggesting that further investigation into the utility of screening for TIM-3 deficiency in extracutaneous SPTCL may be worthwhile to determine if there is diagnostic or prognostic value.

Conclusion

We report an unusual case of subcutaneous panniculitis-like T-cell lymphoma (SPTCL) with clinically occult subcutaneous lesions and prominent biopsy-proven extracutaneous mesenteric involvement and summarize previously reported cases of SPTCL with extracutaneous mesenteric involvement. Similar to three of the previous reported cases of biopsy-proven intra-abdominal SPTCL, the disease appears associated with hemophagocytic lymphohistiocytosis (HLH). Another notable similarity between reported cases of SPTCL having extracutaneous involvement (three biopsy-proven, one not biopsy-proven) and HLH is the aggressive clinical course; our patient was refractory to multi-agent intensive chemotherapy and required stem-cell transplant to achieve remission. Therefore, early detection of extracutaneous lesions with imaging and tissue assessment may be helpful in prognostication of this rare presentation. Our case also illustrates the challenges in establishing a diagnosis of SPTCL, in particular when presented with limited tissue sample due to the aforementioned clinically occult skin involvement. Increased index of suspicion and follow-up biopsies, if needed, are crucial for timely diagnosis. Further investigation is required to better understand the mechanism of disease, prognosis, and optimal treatment approach for SPTCL patients presenting with extracutaneous involvement and HLH.

Data availability Not applicable.

Code availability Not applicable.

Declarations

Ethics approval The University of Alberta Research Ethics Board policies regarding case studies were followed.

Consent to participate Not applicable.

Consent for publication Informed consent was obtained from the patient, including consent to the submission of the case report to this journal.

Conflict of interest The authors declare no competing interests.

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